BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Effectiveness and safety of ivermectin in the treatment of COVID-19: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050532
Article Type:	Protocol
Date Submitted by the Author:	23-Feb-2021
Complete List of Authors:	Machado, Maria; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH) Souza, Amaxsell ; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Pharmacy Linhares, Paula Vívian ; Universidade Potiguar Unidade Salgado Filho, Pharmacy Martins Ferreira, Caio; Universidade Potiguar Unidade Salgado Filho, Biotechnology Graduate Program Franciole, David; Federal University of Rio Grande do Norte, Departament of Nutrition Martins, Rand; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Pharmacy; Cobucci, Ricardo; Universidade Potiguar Unidade Salgado Filho, Biotechnology Graduate Program; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH)
Keywords:	CLINICAL PHARMACOLOGY, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Effectiveness and safety of ivermectin in the treatment of COVID-19: protocol for a systematic review and meta-analysis

Authors: Maria Letícia de Lima Machado [1], Amaxsell Thiago Barros de Souza [2], Paula Vívian Andrade Linhares [3], Caio Fernando Martins Ferreira [4], David Franciole Oliveira Silva [5], Rand Randall Martins [1,2*], Ricardo Ney Cobucci [1,4].

1. Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH), Federal University of Rio Grande do Norte, Natal, Brazil.
2. Department of Pharmacy, Health Sciences Center, Federal University of Rio Grande do Norte, Natal, Brazil.
3. Pharmacy School, Potiguar University, Natal, Brazil.
4. Biotechnology Graduate Program, Potiguar University, Natal, Brazil.
5. Graduate Program in Collective Health, Federal University of Rio Grande do Norte-UFRN, Natal, Brazil.

Mailing address:

Maternidade Escola Januário Cicco, Universidade Federal do Rio Grande do Norte UFRN, Av. General Gustavo Cordeiro de Farias. Petrópolis, Natal-RN 59012-570, Brazil. Phone: +55 84 3342 9824; Fax +55 84 3342 9833.

* Corresponding author

E-mail: randrandall@gmail.com.

Word count: 2.470

For peer review only

ABSTRACT

Introduction

Ivermectin is a drug with antiviral properties and has been proposed as an alternative treatment for patients with coronavirus disease (COVID-19), in some countries; however, there is limited evidence to support its clinical use. Accordingly, the aim of this review and meta-analysis is to obtain superior evidence on the effectiveness and safety of ivermectin in treatment of COVID-19.

Methods and analysis

We will search in the medical databases and International Clinical Trials Registry Platform databases for randomized clinical trials and quasi-randomized trials published from December 2019. The criteria for inclusion are that infection needs to be confirmed by a RT-PCR or serology test, and the effect of ivermectin has been compared with placebo, symptomatic treatment, or no treatment. We will exclude observational studies and clinical trials that involved patients with symptoms suggestive of COVID-19, but without a laboratorial diagnosis. Outcomes of interest include mortality, time to symptom resolution, time of hospitalization, frequency of invasive mechanical ventilation and extracorporeal membrane oxygenation, incidence of SARS, admission to intensive care unit, viral load, PCR-negative status, percentage of infection after prophylactic use, and total incidence of adverse and side effects.

Study selection will follow the PRISMA guidelines. Two reviewers will independently select the studies and assess their eligibility. Two other reviewers will independently extract data from each study. Meta-analysis will then be carried out using a random-effects model, using the mean difference for continuous outcomes and the relative risk or odds ratio for dichotomous outcomes. Bias risk will be assessed using the Cochrane

For peer review only

risk-of-bias tool. The quality of evidence for each outcome will be assessed using GRADE methodology. Review Manager V.5.3.5 will be used for synthesis and subgroup analysis.

Ethics and dissemination

Owing to the nature of the review, ethical approval is not required. The results will be disseminated trough peer-reviewed publications.

Keywords: Ivermectin; COVID-19; SARS-CoV-2; Systematic review

PROSPERO registration number: CRD42020197395

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Evaluation of the efficacy and safety of ivermectin against COVID-19 using only RCT and quasi-RCT data
- Strict search strategy in multiple databases and references of selected studies
- Evidence quality assessment using GRADE working group methodology
- Only a small number of RCTs and quasi-RCTs have evaluated the effectiveness and safety of ivermectin in COVID-19 treatment
- Heterogeneity among patients infected with SARS-CoV-2 and treated with ivermectin can influence the results

Funding:

This work is partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.

Competing Interests:

None declared.

For peer review only

INTRODUCTION

In December 2019, an increase in pneumonia cases was reported in Wuhan, China, and the causative agent was subsequently identified as a new coronavirus (SARS-CoV-2) on January 3, 2020 through tests on secretions from the upper respiratory tract. With the exponential increase in cases of the disease (ultimately termed COVID-19) caused by this virus, the World Health Organization declared a pandemic; by the end of January 2021,102,399,513 cases of infected patients and 2,217,005 deaths due to COVID-19 have been registered worldwide[1]. The scientific community has been working hard to find preventive strategies and effective treatments against SARS-CoV-2, with numerous randomized clinical trials (RCTs) already conducted and others at an advanced stage of testing in humans with medicines and vaccines[2,3,4]. To reduce the risk of severe acute respiratory syndrome (SARS) caused by SARS-CoV-2 and to stimulate the immune system, numerous vaccines have been developed, including mRNA-1237 and CoronaVac, which have been approved for emergency use in some countries[5,6,7,8]. However, to date, there is no evidence of the effectiveness of drugs for the treatment of patients infected with SARS-CoV-2, and results on the efficacy and safety of several vaccines under development are not conclusive[9].

With no confirmed treatment, several countries have adopted a strategy of the off-label use of drugs with potential antiviral and immunomodulatory effects approved for the clinical management of other infections in COVID-19 patients since the beginning of the pandemic[10]. Some studies have evaluated the effectiveness of antivirals and other drugs against COVID-19, including lopinavir/ritonavir, remdesivir, and chloroquine/hydroxychloroquine, with or without azithromycin and

For peer review only

dexamethasone[11,12,13,14,15]. Despite some medications showing positive results, such as dexamethasone, which reduced mortality among inpatients who were receiving mechanical invasive ventilation or oxygen, there is still no drug with proven efficacy for the treatment of COVID-19[15,16].

Caly et al. reported that ivermectin has antiviral activity against SARS-CoV-2 and inhibits its replication *in vitro*[17]. As a result, some countries have proposed the prophylactic use of ivermectin after contact with infected people, or its therapeutic use for those who have been diagnosed with an asymptomatic, mild form of the disease, or in the early stage of COVID-19. Ivermectin is an anti-parasitic agent that causes tonic paralysis of the muscles, thereby inducing the death of the parasite, along with anti-inflammatory activity[18]. Other studies have indicated that ivermectin can inhibit the *in vitro* replication of some RNA viruses such as dengue virus, Zika virus, yellow fever virus, and chikungunya virus[19,20,21,22]. In addition, ivermectin was shown to regulate the immune system, suggesting that it could prevent contracting SARS-CoV-2, even after close contact with an infected individual, as a prophylactic measure[23,24]. However, these results are mainly derived from *in vitro* or observational studies, with only a few RCTs that have evaluated the efficacy and safety of ivermectin in patients with COVID-19 conducted to date.

Brito et al. conducted a systematic review of studies excluding RCTs, and concluded that the effectiveness and safety of ivermectin in patients with COVID-19 has not yet been proven, and its use is not recommended until the results of ongoing clinical trials can be evaluated[9]. Therefore, this protocol describes a systematic review for assessing the efficacy and safety of ivermectin in the prophylaxis and treatment of COVID-19 based on updated data, including those from RCTs.

For peer review only

METHODS AND ANALYSIS

This protocol was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines extension for reporting systematic review protocols (PRISMA-P)[25]. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42020197395.

Research question

Is ivermectin safe and effective for the prophylaxis and treatment of adults infected with SARS-CoV-2?

Inclusion criteria

Participants

This review will include studies that involved adults with SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR) or serological tests, and people at risk of exposure to the virus. Studies including children or patients with only suggestive symptoms of COVID-19, but without a diagnosis confirmed by any of the aforementioned tests, will be excluded.

Intervention

RCTs and quasi randomized clinical trials (quasi-RCTs), one in which participants are allocated to different arms of the trial (to receive the study medicine, or placebo, for example) using a method of allocation that is not truly random, that evaluated the efficacy and safety of ivermectin alone or in combination with other interventions will be considered for inclusion.

There will be no restriction on the dosage, start, and duration of treatment, or route of administration of ivermectin.

For peer review only

Comparator

RCTs and quasi-RCTs that compared ivermectin with placebo, symptomatic treatment, or no treatment will be considered. In addition, studies that included treatment with ivermectin in combination with another treatment will be eligible only if the comparison groups also received a similar co-intervention as the group treated with ivermectin. The comparison groups may have received placebo, symptomatic treatment, or no treatment other than the co-intervention.

Outcome measures

Primary outcome

The primary outcome will be mortality.

Secondary outcomes

Secondary outcomes will be symptom resolution, time of hospitalization (in days), use of invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO), incidence of SARS, admission to the intensive care unit, viral load, PCR-negative status, percentage of infection after prophylactic use, and total incidence of adverse and serious side effects.

Types of studies

We will consider only RCTs and quasi-RCTs.

Article exclusion criteria

Studies with the following features will be excluded: participants diagnosed based solely on symptoms; duplicate, insufficient data, or data that cannot be extracted; observational studies; retrospective studies; non-randomized trials; quasi-experimental studies; and animal studies.

Search strategy

Data from studies that evaluated the efficacy and safety of ivermectin against SARS-CoV-2, published as of December 2019, will be obtained from the electronic databases PubMed, Embase, CENTRAL, Web of Science, Scopus, Cochrane Library, and Google Scholar, and from the clinical trials registries Clinicaltrials.gov, EU Clinical Trials Register, and International Clinical Trials Registry Platform (ICTRP), without language restrictions. Articles will also be searched from the references of the selected studies and from gray literature databases such as OpenGrey.

The following terms with their respective synonyms will be used for database searches: (ivermectin OR stromectol OR mectizan OR MK-933 OR MK 933 OR MK933 OR eqvalan OR ivomec OR soolantra) AND ("COVID-19" OR COVID19 OR "SARS-CoV-2" OR "2019-nCoV" OR "2019-nCoV disease" OR "COVID 19" OR "2019 novel coronavirus infection" OR coronavirus) AND ("randomized clinical trial" OR "controlled clinical trial" OR "randomized controlled trial" OR "intervention study OR "clinical study" OR "clinical studies"). The search strategy that will be used for PubMed is presented in Table 1 as an example.

Table 01 – Pubmed search strategy

	Search items
1	ivermectin
2	stromectol
3	mectizan
4	MK-933
5	MK 933
6	MK933
7	eqvalan
8	Ivomec
9	Soolantra
10	OR/1-9
11	“COVID-19”
12	COVID19
13	“SARS-CoV-2”
14	“2019-nCoV”
15	“2019-nCoV disease”
16	“COVID 19”
17	“2019 novel coronavirus infection”
18	Coronavírus
19	OR/11-18
20	“randomized clinical trial”
21	“controlled clinical trial”
22	“randomized controlled trial”
23	“intervention study”
24	“clinical study”
25	clinical studies
26	OR/20-25
27	10 AND 19 AND 26

For peer review only

Study selection

After searching the databases and references, all identified articles will be exported to the web-based tool Rayyan[26], and duplicates will be removed. In the first stage, titles and abstracts will be reviewed independently by at least two reviewers (MM and AS) based on the inclusion criteria. The full texts of the selected studies will be independently analyzed by two other reviewers (RM and DF); only studies identified by both pairs of reviewers based on the inclusion criteria will ultimately be included in the systematic review, and a third reviewer (RC) will make a final decision for inclusion in the case of discrepancy.

We will maintain a record of the reasons for excluding clinical trials at all stages of review. The results of the selection or exclusion of the studies will be reported using the PRISMA flowchart as shown in Figure 1.

Data extraction

Using standardized forms, two reviewers (AS and DF) will independently extract the following data from each included study: first author; year of publication; study location (country); study design; average age of participants with standard deviation (SD); number of participants; and details about the intervention administered and comparison, including dose and therapeutic scheme, duration, time after diagnosis, route of administration, outcomes assessed, time of their measurement, and adverse effects.

Risk of bias assessment

The risk of bias for each RCT or quasi-RCT will be assessed using the Cochrane tool to assess the risk of bias in randomized studies (RoB 2)[27].

Two reviewers (DF and RM) will independently assess the following five bias domains for all reported results and time points: (1) bias due to the randomization process, (2) deviations from intended interventions (selection and measurement bias), (3) unreported outcome data, (4) presentation of outcomes, and (5) selection of reported results. Thus, the studies will be classified as having a low risk of bias, inconclusive risk, or high risk of bias. Discrepancies between reviewers will be resolved by discussion to reach a consensus; if necessary, a third reviewer (RC) will be consulted. Age, comorbidities (e.g., hypertension, obesity, diabetes), disease severity, and co-interventions will be considered as potential confounding factors.

Measures of treatment effect

For dichotomous variables, we will analyze the relative risk or odds ratios with the respective 95% confidence intervals (CIs). For continuous variables, we will use the mean difference and SD to summarize the data with the 95% CI. In cases in which continuous variables were measured using different scales, the treatment effect will be expressed as the standardized mean difference (SMD) with 95% CI. Wherever possible, we will multiply the SMD by an SD representative of the set of studies, such as the SD of a well-known scale used by several studies included in the analysis on which the result was based. In cases where the minimally important difference (MID) was known, we will present continuous variables in MID units or will report the results as the difference in the proportion of patients who achieved an important minimum effect between intervention and control groups.

Data synthesis

In the event of inclusion of three or more RCTs, we will perform a quantitative synthesis (meta-analysis) using RevMan 5.3.5[28] software with the inverse variance method and a random-effects model if more than 50% heterogeneity is identified among studies. Statistical heterogeneity will be assessed using the I^2 statistic. Subject to insufficient data to calculate an estimated effect, a narrative synthesis will be presented, describing the direction and size of the effects, along with any reported accuracy measures.

Missing data management

We will contact the authors to obtain missing or incomplete data; if unable to obtain the missing data, incomplete data will be excluded from the analysis.

Reporting bias assessment

We will construct funnel plots to evaluate reporting bias if more than 10 RCTs are included. In other cases, Egger's test will be performed to assess publication bias.

Subgroup analysis

We plan to carry out the following subgroup analyses, wherever possible: respiratory failure versus SARS, adults versus elderly people over 65 years old, and prophylactic versus therapeutic use of ivermectin. If a significant difference between subgroups is identified (test for interaction $p<0.05$), we will report the results for individual subgroups separately. We will also perform a formal test for subgroup interactions using RevMan version 5.3.5.

Sensitivity analysis

We will perform a sensitivity analysis to explore the effects of trial bias risk on outcomes, wherever possible. In the case of a significant difference between the estimates of the effect of the primary analysis and sensitivity analysis, we will perform an adjusted sensitivity analysis.

Grading the quality of evidence

The quality of evidence for all outcomes will be assessed using the GRADE[29] Working Group methodology through risk of bias, consistency, objectivity, accuracy, and reported bias. The certainty of evidence will be classified as high, moderate, low, or very low.

DISCUSSION

Ivermectin is a drug with antiviral properties against a few viral infections. Owing to its considerable accessibility due to its low total cost, it has become an alternative treatment for patients with COVID-19. Studies have shown a reduction in mortality in patients hospitalized with COVID-19 who received the drug[23,30]. Another study indicated that early administration of ivermectin resulted in earlier clearance of the virus compared to placebo, assessed over a 5-day course, suggesting that early intervention with ivermectin may limit viral replication in the host[31].

However, there is still no concrete evidence on the efficacy of ivermectin in the prophylaxis and treatment of patients infected with SARS-CoV-2 who are in the initial stage of the disease, or who are already hospitalized after the infection worsens. Thus, it is important to summarize all of evidence, as it becomes available evidence,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

especially robust evidence from RCTs, to assess the effectiveness and safety of ivermectin during different phases of COVID-19.

Siemieniuk et al. performed a systematic review to compare the effectiveness of various drugs used for the treatment of COVID-19, and concluded that corticosteroids reduced the need for mechanical ventilation; however, the effectiveness of azithromycin, remdesivir, hydroxychloroquine, interferon-beta, and tocilizumab has not been proven in the treatment of patients infected with SARS-CoV-2. They did not assess the efficacy and safety of ivermectin. A recent RCT evaluated the effect of early treatment with ivermectin on viral load, in addition to symptomatic and humoral responses in patients with COVID-19[33]. Twenty-four patients were equally randomized to a group that received a single dose of ivermectin and a group that received placebo. The authors concluded that among patients without risk factors for severe COVID-19 who received a single dose of 400 mg/kg of ivermectin, there was no reduction in viral load and no difference in the proportion of a positive PCR test on the seventh day. However, patients treated with ivermectin showed earlier improvement in self-reported anosmia/hyposmia.

Therefore, this systematic review will be carried out using a specific approach with a meta-analysis of the results obtained if there are at least three comparable studies with available data. The current systematic review is justified because of the lack of evidence on the effectiveness and safety of ivermectin in people infected with SARS-CoV-2. The results of this study are expected to provide new insight into the potential effects of ivermectin in adults infected with this new coronavirus, and thus eliminate uncertainties about the treatment that persist despite some related published studies.

For peer review only

PATIENT AND PUBLIC INVOLVEMENT

This research is based on previously conducted studies and does not involve any patients or individuals, or include new studies on human subjects performed by any of the authors.

ETHICS AND DISSEMINATION

Because of the nature of the review, which is a collection of data without direct human involvement, ethical approval is not required. The results will be widely disseminated through peer-reviewed publications, as well as presentations at conferences, congresses, and symposia.

FOOTNOTES

Contributors: RC conceived of the study and provided general guidance for drafting the protocol. AS and DF designed the search strategy. AS, DF, MM, PL, and RM drafted the protocol. RM and RC reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.

Competing interests: None declared.

Patient and public involvement: Patients and/or individuals were not involved in the design, conduct, reporting, or dissemination plans of this research.

Patient consent for publication: Not required.

REFERENCES

1. World Health Organization. WHO; 2021 [30 jan 2021]. Available: http://www.who.int/publications/m/item/weekly-operational-update-on-covid-19

2. Tan WJ, Zhao X, Ma XJ, et al. A novel coronavirus genome identified in a cluster of pneumonia cases — Wuhan, China 2019−2020. China CDC Wkly 2020;2:61-62.

3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.

4. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565-574.

5. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age Ageing. 2020.

6. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403-416.

7. Palacios R, Patiño EG, de Oliveira Piorelli R, et al. Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac – PROFISCOV: A structured summary of a study protocol for a randomised controlled trial.Trials. 2020;21:1-3.

8. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet.2021;21:181-192.

9. Brito GV, Marra LP, Medeiros FC, et al. Ivermectina para a Covid-19. Revisão sistemática rápida. Available: https://oxfordbrazilebm.com/index.php/2020/05/07/ivermectina-para-o-tratamento-de-pacientes-com-covid-19-revisao-sistematica-rapida2/.

10. Sanders JM, Monogue ML, Jodlowski TZ et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA Netw. 2020;323:1824–1836.

11. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med.2020;382:1787-1799.

12. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569-1578.

13. Fiolet T, Guihur A, Rebeaud ME, et al. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Microbiol Infect, 2021;27:19-27.

14. Elavarasi A, Prasad M, Seth T, et al. Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis. J Gen Intern Med. 2020;35:3308–3314.

15. RECOVERY COLLABORATIVE GROUP, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med, 2020.

16. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care. 2020;24:91.

17. Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020; 178:104787.

18. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, et al. The Pharmacokinetics and Interactions of Ivermectin in Humans—A Mini-review. AAPS J. 2008;10:42–46.

19.Tay MY, Fraser JE, Chan WK, et al. Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Res. 2013;99:301-306.

20. Wagstaff KM, Sivakumaran H, Heaton SM, et al. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012;443: 851–856.

21.Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020;177:104760.

22. Varghese FS, Kaukinen P, Gläsker S, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Res. 2016;126: 117-124.

23. Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot. 2020;73: 593–602.

24. Rizzo E. Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. Naunyn Schmiedebergs Arch Pharmacol. 2020;393:1153-1156.

25. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

26. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 2016;5:21

27. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

28. The Nordic Cochrane Centre. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Cochrane Collaboration, 2014.

29. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 201;64:383-394.

30. Rajter JC, Sherman MS, Fatteh N, et al. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The ICON study. Chest. 2021;159:85-92.

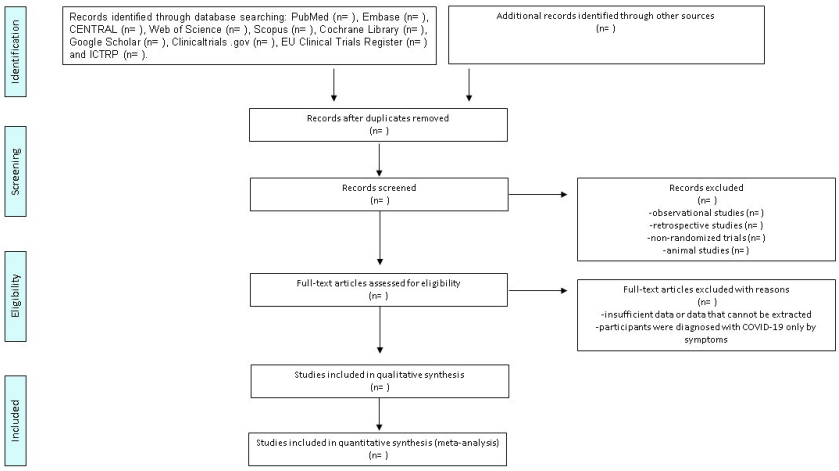
31. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2021:103: 214-216.

32. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980.

33. Chaccour C, Casellas A, Matteo AB, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial.Res Sq. 2020.

Figure 1 - PRISMA flow-chart: search strategy.

For peer review only



PRISMA flow-chart: search strategy

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

For peer review only

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

For peer review only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist:

ADMINISTRATIVE INFORMATION

1. Protocol of a systematic review.
2. PROSPERO registration number : CRD42020197395.
3. **a)** Maria Letícia de Lima Machado 1, Amaxsell Thiago Barros de Souza ², Paula Vívian Andrade Linhares 3, Caio Fernando Martins Ferreira 4, David Franciole Oliveira Silva 5, Rand Randall Martins 1,2*, Ricardo Ney Cobucci 1,4.

1. Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH), Federal University of Rio Grande do Norte, Natal, Brazil.
2. Department of Pharmacy, Health Sciences Center, Federal University of Rio Grande do Norte, Natal, Brazil.
3. Pharmacy School, Potiguar University, Natal, Brazil.
4. Biotechnology Graduate Program, Potiguar University, Natal, Brazil.
5. Graduate Program in Collective Health, Federal University of Rio Grande do Norte-UFRN, Natal, Brazil.

b) Contributors: RC conceived the study and provided general guidance to the drafting of the protocol. AS, DF and PL drafted the protocol. AS and DF designed the search strategy. AS, DF, MM,PL and RM drafted the manuscript. RM and RC reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript. Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.

4. Not applicable.
5. a) Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.
b) Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.
c) Not applicable.

INTRODUCTION

6. The current systematic review is justified due to the fact that there is lack of evidence on the effectiveness and safety of ivermectin in people infected with SARS-Cov-2. The results of this study are expected to speculate the potential effects of ivermectin in adults infected with the new coronavirus, and thus eliminating uncertainties about the treatment that persist despite some related published studies.

7. This systematic review protocol aims to assess the efficacy and safety of Ivermectin in the prophylaxis and treatment of COVID-19.

METHODS

8. p. 6-7

For peer review only

9. p.8

10. Data of the studies that evaluated the efficacy and safety of ivermectin against SARS-CoV-2, published since December 2019, were obtained from the electronic databases (PubMed).

11. **a)**p.10
b) p.11
c) p.12

12. p.6-8

13. p.7

14. p.10-11

15. **a)** p.12-13
b) p. 12-13
c) p. 12-13
d) p. 12-13

16. p.6-12-13

17. The quality of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE), through the domains of risk of bias, consistency, objectivity, accuracy and reported biases. The certainty of evidence will be classified as high, moderate, low or very low.

For peer review only

BMJ Open

Effectiveness and safety of ivermectin in the treatment of COVID-19: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050532.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Aug-2021
Complete List of Authors:	Machado, Maria; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH) Souza, Amaxsell ; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Pharmacy Linhares, Paula Vívian ; Universidade Potiguar Unidade Salgado Filho, Pharmacy Martins Ferreira, Caio; Universidade Potiguar Unidade Salgado Filho, Biotechnology Graduate Program Franciole, David; Federal University of Rio Grande do Norte, Departament of Nutrition Martins, Rand; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Pharmacy; Cobucci, Ricardo; Universidade Potiguar Unidade Salgado Filho, Biotechnology Graduate Program; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH)
Primary Subject Heading:	Global health
Secondary Subject Heading:	Infectious diseases
Keywords:	CLINICAL PHARMACOLOGY, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Effectiveness and safety of ivermectin in the treatment of COVID-19: protocol for a systematic review and meta-analysis

Authors: Maria Letícia de Lima Machado [1], Amaxsell Thiago Barros de Souza [2], Paula Vívian Andrade Linhares [3], Caio Fernando Martins Ferreira [5], David Franciole Oliveira Silva [4], Rand Randall Martins [1,2*], Ricardo Ney Cobucci [1,5].

1. Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH), Federal University of Rio Grande do Norte, Natal, Brazil.
2. Department of Pharmacy, Health Sciences Center, Federal University of Rio Grande do Norte, Natal, Brazil.
3. Pharmacy School, Potiguar University, Natal, Brazil.
4. Graduate Program in Collective Health, Federal University of Rio Grande do Norte-UFRN, Natal, Brazil.
5. Biotechnology Graduate Program, Potiguar University, Natal, Brazil.

Mailing address:

Maternidade Escola Januário Cicco, Universidade Federal do Rio Grande do Norte UFRN, Av. General Gustavo Cordeiro de Farias. Petrópolis, Natal-RN 59012-570, Brazil. Phone: +55 84 3342 9824; Fax +55 84 3342 9833.

* Corresponding author

E-mail: randrandall@gmail.com.

Word count: 2.470

For peer review only

ABSTRACT

Introduction

Ivermectin is a drug with antiviral properties and has been proposed as an alternative treatment for patients with coronavirus disease (COVID-19), in some countries; however, there is limited evidence to support its clinical use. Accordingly, the aim of this review and meta-analysis is to obtain superior evidence on the effectiveness and safety of ivermectin in treatment of COVID-19.

Methods and analysis

We will search in the medical databases and International Clinical Trials Registry Platform databases for randomized clinical trials and quasi-randomized trials published from December 2019. The criteria for inclusion are that infection needs to be confirmed by a RT-PCR or serology test, and the effect of ivermectin has been compared with placebo, symptomatic treatment, or no treatment. We will exclude observational studies and clinical trials that involved patients with symptoms suggestive of COVID-19, but without a laboratorial diagnosis. Outcomes of interest include mortality, time to symptom resolution, time of hospitalization, frequency of invasive mechanical ventilation and extracorporeal membrane oxygenation, incidence of SARS, admission to intensive care unit, viral load, PCR-negative status, percentage of infection after prophylactic use, and total incidence of adverse and side effects. Study selection will follow the PRISMA guidelines. Two reviewers will independently select the studies and assess their eligibility. Two other reviewers will independently extract data from each study. Meta-analysis will then be carried out using fixed or random effects model, using the mean difference for continuous outcomes and the relative risk for dichotomous outcomes. Bias risk will be assessed using the Cochrane

For peer review only

risk-of-bias tool. The quality of evidence for each outcome will be assessed using GRADE methodology. Review Manager V.5.3.5 will be used for synthesis and subgroup analysis.

Ethics and dissemination

Owing to the nature of the review, ethical approval is not required. The results will be disseminated trough peer-reviewed publications.

Keywords: Ivermectin; COVID-19; SARS-CoV-2; Systematic review

PROSPERO registration number: CRD42020197395

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Evaluation of the efficacy and safety of ivermectin against COVID-19 using only RCT and quasi-RCT data
- Strict search strategy in multiple databases and references of selected studies
- Evidence quality assessment using GRADE working group methodology
- Only a small number of RCTs and quasi-RCTs have evaluated the effectiveness and safety of ivermectin in COVID-19 treatment
- Heterogeneity among patients infected with SARS-CoV-2 and treated with ivermectin can influence the results

Funding:

This work is partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.

Competing Interests:

None declared.

For peer review only

INTRODUCTION

In December 2019, an increase in pneumonia cases was reported in Wuhan, China, and the causative agent was subsequently identified as a new coronavirus (SARS-CoV-2) on January 3, 2020 through tests on secretions from the upper respiratory tract. With the exponential increase in cases of the disease (ultimately termed COVID-19) caused by this virus, the World Health Organization declared a pandemic; by the end of January 2021,102,399,513 cases of infected patients and 2,217,005 deaths due to COVID-19 have been registered worldwide [1]. The scientific community has been working hard to find preventive strategies and effective treatments against SARS-CoV-2, with numerous randomized clinical trials (RCTs) already conducted and others at an advanced stage of testing in humans with medicines and vaccines [2-4]. To reduce the risk of severe acute respiratory syndrome (SARS) caused by SARS-CoV-2 and to stimulate the immune system, numerous vaccines have been developed, including mRNA-1237 and CoronaVac, which have been approved for emergency use in some countries [5-8]. However, to date, there is no evidence of the effectiveness of drugs for the treatment of patients infected with SARS-CoV-2, and results on the efficacy and safety of several vaccines under development are not conclusive [9].

With no confirmed treatment, several countries have adopted a strategy of the off-label use of drugs with potential antiviral and immunomodulatory effects approved for the clinical management of other infections in COVID-19 patients since the beginning of the pandemic [10]. Some studies have evaluated the effectiveness of antivirals and other drugs against COVID-19, including lopinavir/ritonavir, remdesivir, and chloroquine/hydroxychloroquine, with or without azithromycin and

For peer review only

dexamethasone [11-15]. Despite some medications showing positive results, such as dexamethasone, which reduced mortality among inpatients who were receiving mechanical invasive ventilation or oxygen, there is still no drug with proven efficacy for the treatment of COVID-19 [15, 16].

Caly et al. reported that ivermectin has antiviral activity against SARS-CoV-2 and inhibits its replication *in vitro* [17]. As a result, some countries have proposed the prophylactic use of ivermectin after contact with infected people, or its therapeutic use for those who have been diagnosed with an asymptomatic, mild form of the disease, or in the early stage of COVID-19. Ivermectin is an anti-parasitic agent that causes tonic paralysis of the muscles, thereby inducing the death of the parasite, along with anti-inflammatory activity [18]. Other studies have indicated that ivermectin can inhibit the *in vitro* replication of some RNA viruses such as dengue virus, Zika virus, yellow fever virus, and chikungunya virus [19-22]. In addition, ivermectin was shown to regulate the immune system, suggesting that it could prevent contracting SARS-CoV-2, even after close contact with an infected individual, as a prophylactic measure [23, 24]. However, these results are mainly derived from *in vitro* or observational studies, with only a few RCTs that have evaluated the efficacy and safety of ivermectin in patients with COVID-19 conducted to date.

Brito et al. conducted a systematic review of studies excluding RCTs and concluded that the effectiveness and safety of ivermectin in patients with COVID-19 has not yet been proven, and its use is not recommended until the results of ongoing clinical trials can be evaluated [9]. Therefore, this protocol describes a systematic review for assessing the efficacy and safety of ivermectin in the prophylaxis and treatment of COVID-19 based on updated data, including those from RCTs.

For peer review only

METHODS AND ANALYSIS

This protocol was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines extension for reporting systematic review protocols (PRISMA-P) [25]. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42020197395.

Research question

Is ivermectin safe and effective for the prophylaxis and treatment of adults infected with SARS-CoV-2?

Inclusion criteria

Participants

This review will include studies that involved adults with SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR) or serological tests, and people at risk of exposure to the virus (people having “high-risk” contact with patients with confirmed COVID-19). Studies including children or patients with only suggestive symptoms of COVID-19, but without a diagnosis confirmed by any of the aforementioned tests, will be excluded.

Intervention

RCTs and quasi randomized clinical trials (quasi-RCTs), one in which participants are allocated to different arms of the trial (to receive the study medicine, or placebo, for example) using a method of allocation that is not truly random, that

For peer review only

evaluated the efficacy and safety of ivermectin alone or in combination with other interventions will be considered for inclusion.

There will be no restriction on the dosage, start, and duration of treatment, or route of administration of ivermectin.

Comparator

RCTs and quasi-RCTs that compared ivermectin with placebo, symptomatic treatment, or no treatment will be considered. In addition, studies that included treatment with ivermectin in combination with another treatment will be eligible only if the comparison groups also received a similar co-intervention as the group treated with ivermectin. The comparison groups may have received placebo, symptomatic treatment, or no treatment other than the co-intervention.

Outcome measures

Primary outcome

The primary outcome will be mortality.

Secondary outcomes

Secondary outcomes will be symptom resolution, time of hospitalization (in days), use of invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO), incidence of SARS, admission to the intensive care unit, viral load, PCR-negative status, percentage of infection after prophylactic use, and total incidence of adverse and serious side effects.

Types of studies

We will consider only RCTs and quasi-RCTs.

For peer review

Article exclusion criteria

Studies with the following features will be excluded: participants diagnosed based solely on symptoms; duplicate, insufficient data, or data that cannot be extracted; observational studies; retrospective studies; non-randomized trials; quasi-experimental studies; and animal studies.

Search strategy

Data from studies that evaluated the efficacy and safety of ivermectin against SARS-CoV-2, published as of December 2019, will be obtained from the electronic databases PubMed, Embase, CENTRAL, Web of Science, Scopus, Cochrane Library, and Google Scholar, and from the clinical trials registries Clinicaltrials.gov, EU Clinical Trials Register, and International Clinical Trials Registry Platform (ICTRP), without language restrictions. Articles will also be searched from the references of the selected studies and from gray literature databases such as OpenGrey.

The following terms with their respective synonyms will be used for database searches: (ivermectin OR stromectol OR mectizan OR MK-933 OR MK 933 OR MK933 OR eqvalan OR ivomec OR soolantra) AND (“COVID-19” OR COVID19 OR “SARS-CoV-2” OR “2019-nCoV” OR “2019-nCoV disease” OR “COVID 19” OR “2019 novel coronavirus infection” OR coronavirus) AND (“randomized clinical trial” OR “controlled clinical trial” OR “randomized controlled trial” OR “intervention study OR “clinical study” OR “clinical studies”). The search strategy that will be used for PubMed is presented in Table 1 as an example.

Table 1: PubMed search strategy

	Search items
1	ivermectin
2	stromectol
3	mectizan
4	MK-933
5	MK 933
6	MK933
7	eqvalan
8	Ivomec
9	Soolantra
10	OR/1-9
11	“COVID-19”
12	COVID19
13	“SARS-CoV-2”
14	“2019-nCoV”
15	“2019-nCoV disease”
16	“COVID 19”
17	“2019 novel coronavirus infection”
18	Coronavírus
19	OR/11-18
20	“randomized clinical trial”
21	“controlled clinical trial”
22	“randomized controlled trial”
23	“intervention study”
24	“clinical study”
25	clinical studies

For peer review only

26	OR/20-25
27	10 AND 19 AND 26

Study selection

After searching the databases and references, all identified articles will be exported to the web-based tool Rayyan [26], and duplicates will be removed. In the first stage, titles and abstracts will be reviewed independently by at least two reviewers (MM and AS) based on the inclusion criteria. The full texts of the selected studies will be independently analyzed by two other reviewers (RM and DF); only studies identified by both pairs of reviewers based on the inclusion criteria will ultimately be included in the systematic review, and a third reviewer (RC) will make a final decision for inclusion in the case of discrepancy.

We will maintain a record of the reasons for excluding clinical trials at all stages of review. The results of the selection or exclusion of the studies will be reported using the PRISMA flowchart as shown in Figure 1.

Data extraction

Using standardized forms, two reviewers (AS and DF) will independently extract the following data from each included study: first author; year of publication; study location (country); study design; average age of participants with standard deviation (SD); number of participants; and details about the intervention administered and comparison, including dose and therapeutic scheme, duration, time after diagnosis,

route of administration, outcomes assessed, time of their measurement, and adverse effects.

Risk of bias assessment

The risk of bias for each RCT or quasi-RCT will be assessed using the Cochrane tool to assess the risk of bias in randomized studies (RoB 2) [27].

Two reviewers (DF and RM) will independently assess the following five bias domains for all reported results and time points: (1) bias due to the randomization process, (2) deviations from intended interventions (selection and measurement bias), (3) unreported outcome data, (4) presentation of outcomes, and (5) selection of reported results. Thus, the studies will be classified as having a low risk of bias, inconclusive risk, or high risk of bias. Discrepancies between reviewers will be resolved by discussion to reach a consensus; if necessary, a third reviewer (RC) will be consulted. Age, comorbidities (e.g., hypertension, obesity, diabetes), disease severity, and co-interventions will be considered as potential confounding factors.

Measures of treatment effect

For dichotomous variables, we will analyze the relative risk (RR) with the respective 95% confidence intervals (CIs). For continuous variables, we will use the mean difference and SD to summarize the data with the 95% CI. In cases in which continuous variables were measured using different scales, the treatment effect will be expressed as the standardized mean difference (SMD) with 95% CI. Wherever possible, we will multiply the SMD by an SD representative of the set of studies, such as the SD of a well-known scale used by several studies included in the analysis on which the result was based. In cases where the minimally important difference (MID)

was known, we will present continuous variables in MID units or will report the results as the difference in the proportion of patients who achieved an important minimum effect between intervention and control groups.

Data synthesis

In the event of inclusion of three or more RCTs, we will perform a quantitative synthesis (meta-analysis) using RevMan 5.3.5 [28] software with the fixed-effects or random-effects model if more than 50% heterogeneity is identified among studies. Statistical heterogeneity will be assessed using the I^2 statistic. Subject to insufficient data to calculate an estimated effect, a narrative synthesis will be presented, describing the direction and size of the effects, along with any reported accuracy measures.

Missing data management

We will contact the authors to obtain missing or incomplete data; if unable to obtain the missing data, incomplete data will be excluded from the analysis.

Reporting bias assessment

We will construct funnel plots to evaluate reporting bias if more than 10 RCTs are included. In other cases, Egger's test will be performed to assess publication bias.

Subgroup analysis

We plan to carry out the following subgroup analyses, wherever possible: respiratory failure versus SARS, adults versus elderly people over 65 years old, and

prophylactic versus therapeutic use of ivermectin. If a significant difference between subgroups is identified (test for interaction $p<0.05$), we will report the results for individual subgroups separately. We will also perform a formal test for subgroup interactions using RevMan version 5.3.5.

Sensitivity analysis

We will perform a sensitivity analysis to explore the effects of trial bias risk on outcomes, wherever possible. The primary analysis will include only those studies that had low risk or some concerns of bias according to the RoB 2 assessment. We will include high risk of bias studies in a secondary analysis to assess the impact on the results.

In the case of a significant difference between the estimates of the effect of the primary analysis and sensitivity analysis, we will perform an adjusted sensitivity analysis.

Grading the quality of evidence

The quality of evidence for all outcomes will be assessed using the GRADE [29] Working Group methodology through risk of bias, consistency, objectivity, accuracy, and reported bias. The certainty of evidence will be classified as high, moderate, low, or very low.

DISCUSSION

Ivermectin is a drug with antiviral properties against a few viral infections. Owing to its considerable accessibility due to its low total cost, it has become an alternative treatment for patients with COVID-19. Studies have shown a reduction in mortality in patients hospitalized with COVID-19 who received the drug [23, 30]. Another study indicated that early administration of ivermectin resulted in earlier clearance of the virus compared to placebo, assessed over a 5-day course, suggesting that early intervention with ivermectin may limit viral replication in the host [31].

However, there is still no concrete evidence on the efficacy of ivermectin in the prophylaxis and treatment of patients infected with SARS-CoV-2 who are in the initial stage of the disease, or who are already hospitalized after the infection worsens. Thus, it is important to summarize all of evidence, as it becomes available evidence, especially robust evidence from RCTs, to assess the effectiveness and safety of ivermectin during different phases of COVID-19.

Siemieniuk et al. performed a systematic review to compare the effectiveness of various drugs used for the treatment of COVID-19, and concluded that corticosteroids reduced the need for mechanical ventilation; however, the effectiveness of azithromycin, remdesivir, hydroxychloroquine, interferon-beta, and tocilizumab has not been proven in the treatment of patients infected with SARS-CoV-2. They did not assess the efficacy and safety of ivermectin [32]. A recent RCT evaluated the effect of early treatment with ivermectin on viral load, in addition to symptomatic and humoral responses in patients with COVID-19 [33]. Twenty-four patients were equally randomized to a group that received a single dose of ivermectin and a group that received placebo. The authors concluded that among patients without

For peer review only

risk factors for severe COVID-19 who received a single dose of 400 mg/kg of ivermectin, there was no reduction in viral load and no difference in the proportion of a positive PCR test on the seventh day. However, patients treated with ivermectin showed earlier improvement in self-reported anosmia/hyposmia.

A possible limitation of this study is that clinical trials with low number of participants, or events, or both, leading to wide confidence intervals and high uncertainty of the estimated effects can compromise the level of evidence generated in this meta-analysis.

Therefore, this systematic review will be carried out using a specific approach with a meta-analysis of the results obtained if there are at least three comparable studies with available data. The current systematic review is justified because of the lack of evidence on the effectiveness and safety of ivermectin in people infected with SARS-CoV-2. The results of this study are expected to provide new insight into the potential effects of ivermectin in adults infected with this new coronavirus, and thus eliminate uncertainties about the treatment that persist despite some related published studies.

For peer review only

PATIENT AND PUBLIC INVOLVEMENT

This research is based on previously conducted studies and does not involve any patients or individuals or include new studies on human subjects performed by any of the authors.

ETHICS AND DISSEMINATION

Because of the nature of the review, which is a collection of data without direct human involvement, ethical approval is not required. The results will be widely disseminated through peer-reviewed publications, as well as presentations at conferences, congresses, and symposia.

FOOTNOTES

Contributors: RC conceived of the study and provided general guidance for drafting the protocol. AS and DF designed the search strategy. AS, CM, DF, MM, PL, and RM drafted the protocol. RM and RC reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.

Competing interests: None declared.

Patient and public involvement: Patients and/or individuals were not involved in the design, conduct, reporting, or dissemination plans of this research.

Patient consent for publication: Not required.

REFERENCES

1. World Health Organization. WHO; 2021 [30 jan 2021]. Available: http://www.who.int/publications/m/item/weekly-operational-update-on-covid-19

2. Tan WJ, Zhao X, Ma XJ, et al. A novel coronavirus genome identified in a cluster of pneumonia cases — Wuhan, China 2019−2020. China CDC Wkly 2020;2:61-62.

3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.

4. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565-574.

5. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age Ageing. 2020.

6. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403-416.

7. Palacios R, Patiño EG, de Oliveira Piorelli R, et al. Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac – PROFISCOV: A structured summary of a study protocol for a randomised controlled trial.Trials. 2020;21:1-3.

8. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet.2021;21:181-192.

9. Brito GV, Marra LP, Medeiros FC, et al. Ivermectina para a Covid-19. Revisão sistemática rápida. Available: https://oxfordbrazilebm.com/index.php/2020/05/07/ivermectina-para-o-tratamento-de-pacientes-com-covid-19-revisao-sistematica-rapida2/.

10. Sanders JM, Monogue ML, Jodlowski TZ et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA Netw. 2020;323:1824–1836.

11. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med.2020;382:1787-1799.

12. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569-1578.

13. Fiolet T, Guihur A, Rebeaud ME, et al. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Microbiol Infect, 2021;27:19-27.

14. Elavarasi A, Prasad M, Seth T, et al. Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis. J Gen Intern Med. 2020;35:3308–3314.

15. RECOVERY COLLABORATIVE GROUP, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med, 2020.

16. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care. 2020;24:91.

17. Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020; 178:104787.

18. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, et al. The Pharmacokinetics and Interactions of Ivermectin in Humans—A Mini-review. AAPS J. 2008;10:42–46.

19.Tay MY, Fraser JE, Chan WK, et al. Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Res. 2013;99:301-306.

20. Wagstaff KM, Sivakumaran H, Heaton SM, et al. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012;443: 851–856.

21.Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Res. 2020;177:104760.

22. Varghese FS, Kaukinen P, Gläsker S, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Res. 2016;126: 117-124.

23. Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiot. 2020;73: 593–602.

24. Rizzo E. Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. Naunyn Schmiedebergs Arch Pharmacol. 2020;393:1153-1156.

25. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

26. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 2016;5:21

27. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

28. The Nordic Cochrane Centre. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Cochrane Collaboration, 2014.

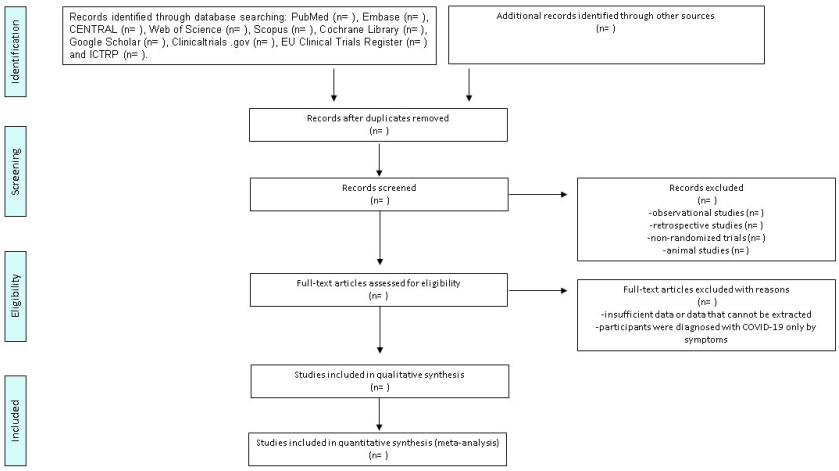
29. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 201;64:383-394.

30. Rajter JC, Sherman MS, Fatteh N, et al. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: The ICON study. Chest. 2021;159:85-92.

31. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2021:103: 214-216.

32. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980.

33. Chaccour C, Casellas A, Matteo AB, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial.Res Sq. 2020.



PRISMA flow-chart: search strategy

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist:

ADMINISTRATIVE INFORMATION

1. Protocol of a systematic review.
2. PROSPERO registration number : CRD42020197395.
3. **a)** Maria Letícia de Lima Machado 1, Amaxsell Thiago Barros de Souza [2], Paula Vívian Andrade Linhares 3, Caio Fernando Martins Ferreira 4, David Franciole Oliveira Silva 5, Rand Randall Martins 1,2*, Ricardo Ney Cobucci 1,4.

1. Graduate Program in Sciences Applied to Women's Health, Maternidade Escola Januário Cicco (MEJC/EBSERH), Federal University of Rio Grande do Norte, Natal, Brazil.
2. Department of Pharmacy, Health Sciences Center, Federal University of Rio Grande do Norte, Natal, Brazil.
3. Pharmacy School, Potiguar University, Natal, Brazil.
4. Biotechnology Graduate Program, Potiguar University, Natal, Brazil.
5. Graduate Program in Collective Health, Federal University of Rio Grande do Norte-UFRN, Natal, Brazil.

b) Contributors: RC conceived the study and provided general guidance to the drafting of the protocol. AS, DF and PL drafted the protocol. AS and DF designed the search strategy. AS, DF, MM,PL and RM drafted the manuscript. RM and RC reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript. Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.

4. Not applicable.
5. a) Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.
b) Funding: This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Finance Code 001.
c) Not applicable.

INTRODUCTION

6. The current systematic review is justified due to the fact that there is lack of evidence on the effectiveness and safety of ivermectin in people infected with SARS-Cov-2. The results of this study are expected to speculate the potential effects of ivermectin in adults infected with the new coronavirus, and thus eliminating uncertainties about the treatment that persist despite some related published studies.

7. This systematic review protocol aims to assess the efficacy and safety of Ivermectin in the prophylaxis and treatment of COVID-19.

METHODS

8. p. 6-7

For peer review only

9. p.8

10. Data of the studies that evaluated the efficacy and safety of ivermectin against SARS-CoV-2, published since December 2019, were obtained from the electronic databases (PubMed).

11. **a)**p.10
b) p.11
c) p.12

12. p.6-8

13. p.7

14. p.10-11

15. **a)** p.12-13
b) p. 12-13
c) p. 12-13
d) p. 12-13

16. p.6-12-13

17. The quality of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE), through the domains of risk of bias, consistency, objectivity, accuracy and reported biases. The certainty of evidence will be classified as high, moderate, low or very low.

For peer review only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

For peer review only

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

For peer review only